

## Development of a Model-Based Clinical Sepsis Biomarker for Critically Ill Patients

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**Abstract:** Sepsis occurs frequently in the intensive care unit (ICU) and is a leading cause of admission, mortality, and cost. Treatment guidelines recommend early intervention, however positive blood culture results may take up to 48 hours. Insulin sensitivity ( $S_I$ ) is known to decrease with worsening condition and could thus be used to aid diagnosis. Some glycemic control protocols are able to accurately identify insulin sensitivity in real-time.

Receiver operator characteristic (ROC) curves and cut-off  $S_I$  values for sepsis diagnosis were calculated for real-time model-based insulin sensitivity from glycemic control data of 36 patients with sepsis. Patients were identified as having sepsis based on a clinically validated sepsis score (ss) of 2 or higher (ss = 0-4 for increasing severity). A clinical biomarker was calculated from patient clinical data to maximize the discrimination between cohorts.

Insulin sensitivity as a sepsis biomarker for diagnosis of severe sepsis achieves a 50% sensitivity, 76% specificity, 4.8% PPV, and 98.3% NPV at a  $S_I$  cut-off value of  $0.00013 \text{ L}^* \text{mU min}^{-1}$ . A clinical biomarker combining  $S_I$ , temperature, heart rate, respiratory rate, blood pressure, and their respective hourly rates of change achieves 73% sensitivity, 80% specificity, 8.4% PPV, and 99.2% NPV. Thus, a clinical biomarker provides an effective real-time negative predictive diagnostic for severe sepsis. Examination of both inter- and intra-patient statistical distribution of this biomarker and sepsis score show potential avenues to improve the positive predictive value.

**Keywords:** sepsis, insulin sensitivity, biomarker, diagnosis, receiver operator characteristic, glucose control, real-time clinical application.

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### 1. INTRODUCTION

Sepsis presents a serious medical problem in the adult intensive care unit (ICU), with a 11-15% incidence of severe sepsis, 30-60% mortality rate, \$22,100 USD average cost per case, \$16.7 billion USD annual total cost, and 1.5% projected annual incidence increase (Angus et al., 2001). Sepsis treatment guidelines and patient management protocols recommend early goal-directed resuscitation of the septic patient during the first 6 hours after infection recognition (Dellinger et al., 2008). Currently, blood bacteria cultures are considered the gold standard for confirmation of infection. However, only 51% of sepsis cases are positively identified as cultured pathogens (Martin et al., 2003).

Early interventions have been documented to reduce mortality from 46.5% to 30.5% (Rivers et al., 2001). In addition, a landmark clinical trial implementing a blood glucose control protocol resulted in a reduction in the incidence of sepsis (Van den Berghe et al., 2001). Currently available biomarkers, such as procalcitonin (PCT), provide sepsis diagnostic test results in 2-3 hours with commercially

available kits, but to various levels of clinical accuracy (Carrigan et al., 2004).

A clinically validated glucose-insulin model that is able to model insulin sensitivity ( $S_I$ ) in real-time has been used to develop blood glucose protocols for critically ill patients (Chase et al., 2007b, Lonergan et al., 2006). An integral-based parameter identification method has been used to fit the data (Hann et al., 2005). The model-based  $S_I$  has been observed to indicate the severity of illness and metabolic status, as well as being validated against euglycaemic clamp data (Lotz et al., 2006). Insulin sensitivity has also been previously documented as decreasing with worsening condition (Chambrier et al., 2000), and increasing with improvement (Chase et al., 2008, Langouche et al., 2007).

This study aims to evaluate the relationship of modelled insulin sensitivity (Lin, 2006, Lonergan et al., 2006) and patient condition. In particular, this study examines using the modelled insulin sensitivity as a marker for real-time diagnosis and differentiation of Systemic Inflammatory Response Syndrome (SIRS) and sepsis in a cohort of adult ICU patients. It extends the work of Blakemore et al. (2008)

by increasing discrimination and utilizing additional clinical measurements.

## 2. METHODS

### 2.1 Physiological glucose-insulin model

The physiological glucose-insulin model for clinically ill patients has one compartment for plasma glucose, two compartments for insulin kinetics, and a two-compartment dextrose absorption model.

$$\dot{G} = -p_G G - S_I G \frac{Q}{1 + \alpha_G Q} + \frac{P(t)EGP_{\max} - CNS}{V_G(t)} \quad (1)$$

$$\dot{Q} = -kQ + kI \quad (2)$$

$$\dot{I} = -\frac{nI}{1 + \alpha_I I} + \frac{u_{ex}(t)}{V_I} + e^{-k_I u_{ex}(t)} I_B \quad (3)$$

$$\dot{P1} = -d_1 P1 + D(t) \quad (4)$$

$$\dot{P2} = -\min(d_2 P2, P_{\max}) + d_1 P(1) \quad (5)$$

$$P(t) = \min(d_2 P2, P_{\max}) \quad (6)$$

In this model,  $G$  is the blood glucose level,  $I$  is the plasma insulin, and  $Q$  is the interstitial insulin.  $EGP_{\max}$  is the theoretical maximum endogenous glucose production for a patient under no presence of glucose or insulin. Endogenous glucose production ( $EGP$ ) is suppressed with increasing  $G$  and  $Q$ . Insulin independent glucose removal (excluding central nervous system uptake  $CNS$ ) and the suppression of  $EGP$  from  $EGP_{\max}$  with respect to  $G$  are represented with  $p_G$ . In contrast, insulin mediated glucose removal and the suppression of  $EGP$  from  $EGP_{\max}$  due to GLUT4 (which action is associated with the compounding effect of receptor-binding insulin and blood glucose) is represented with  $S_I$ .

Insulin sensitivity ( $S_I$ ) is time varying and reflects evolving patient condition. Exogenous inputs are enteral dextrose infusion  $D(t)$  and insulin administration  $u_{ex}(t)$ . Compartment  $P1$  represents the stomach, and  $P2$  represents the gut. Glucose appearance,  $P(t)$  from input  $D(t)$  is the flux of glucose transport out of the gut,  $P2$ . This flux is saturable, and the maximal out flux is  $P_{\max}$ . All other associated parameters are physiologically defined transport rates ( $n$ ,  $k$ ,  $d_1$ ,  $d_2$ ), saturation parameters ( $\alpha_G$ ,  $\alpha_I$ ), or volumes ( $V_G$ ,  $V_I$ ).

### 2.2 Sepsis score (ss) criteria and analysis

Sepsis is a systemic inflammatory response syndrome (SIRS) due to infection (Bone, 1992). In this study, sepsis is defined using the clinical classification score (ss) provided by the ACCP/SCCM guideline definitions (Levy et al., 2003). The criteria are defined in Tables 1-3, which include SIRS and the Sepsis-related Organ Failure Assessment (SOFA) score (Vincent et al., 1996).

**Table 1. SIRS criteria**

score	Criteria	
+ 1	temperature	< 36° C > 38° C
+ 1	heart rate	> 90/min
+ 1	respiratory rate or PaCO <sub>2</sub>	> 20/min < 32 mm Hg
+ 1	white blood cell count	< 4 x 10 <sup>9</sup> /L or > 12 x 10 <sup>9</sup> /L or presence of > 10% immature granulocytes

**Table 2. SOFA criteria**

score	system	criteria	
+ 1	cardiovascular	MAP <sup>a</sup> or need for inotropes	< 60 mm Hg
+ 1	respiratory	PaO <sub>2</sub> /FiO <sub>2</sub>	<250 mm Hg/mm Hg <200 mm Hg/mm Hg with pneumonia
+ 1	renal	urine output	< 0.5 ml/kg/h
+ 1	blood	platelets	< 80 x 10 <sup>9</sup> /L or 50% drop in 3 days

<sup>a</sup>Mean arterial pressure

Clinical data was gathered for  $n = 36$  sepsis patients admitted to the medical ICU in Christchurch Hospital (Christchurch, New Zealand). Each patient was on the SPRINT blood glucose control protocol (Chase et al., 2008), providing 9208 total patient hours of hourly modelled insulin sensitivity. The hourly  $S_I$  was compared to SIRS and ss data. Note that each stay included periods of sepsis and without sepsis (ss = 0). These periods are differentiated by positive blood culture and SIRS  $\geq 2$ , and thus ss  $\geq 1$ .

**Table 3. Sepsis score (ss) criteria**

sepsis score	SIRS > 2	Infection during stay	organ failure > 1	fluid resuscitation	inotrope present	high inotrope dose <sup>a</sup>
0 normal						
1 sepsis	X	X				
2 severe sepsis	X	X	X	X		
3 septic shock	X	X	X	X	X	
4 refractory septic shock	X	X	X	X	X	X

<sup>a</sup>adrenaline or noradrenaline > 0.2 mg min<sup>-1</sup> kg<sup>-1</sup>

Receiver Operator Characteristic (ROC) curves were used to examine the performance of  $S_I$  as a diagnostic marker for sepsis. ROC curves effectively examine the ability of the biomarker to differentiate between populations. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also evaluated. ROC curves effectively examine the separation between normal and diseased populations in terms of probability density functions (PDF). Variability of ss score from one hour to the next hour were also examined.

Therefore, other clinical measurements were evaluated and combined with  $S_I$  to create a biomarker that aims to maximise the PDF separation or discrimination in normal and septic groups. The biomarker was created as an hourly changing function based on hourly  $S_I$  and clinical measurements. A linear recursive least square method was used to maximize the discrimination between populations. The specific goal was to provide discrimination for  $ss \geq 2$ , where prior studies (Blakemore et al., 2008) only achieved it for  $ss \geq 3$ . Achieving this goal for the lower  $ss = 2$  value will provide a marker for a far larger group of patients.

### 3. RESULTS AND DISCUSSION

Table 4 shows the total hours at each sepsis score. The majority of the hours are at  $ss < 2$ .

**Table 4. Patient hours by sepsis score (ss)**

sepsis score (ss)	0	1	2	3	4
patient hours	4186 (45.1%)	4861 (52.3%)	91 (1.0%)	88 (0.9%)	60 (0.6%)

#### 3.1 Insulin sensitivity ( $S_I$ ) and sepsis score (ss)

Figure 1 shows a cumulative distribution function (CDF) plot of  $S_I$  for each ss group.  $S_I$  is generally lower for more severe sepsis. However, the distinction between the septic ( $ss \geq 1$ ) and non-septic ( $ss = 0$ ) groups is not clear.

#### 3.2 $S_I$ biomarker

Figure 2 shows the ROC curve for  $S_I$  as a sepsis biomarker. There is minimal discrimination between no sepsis ( $ss = 0$ ) and a sepsis score of  $ss = 1$ . For  $ss \geq 2$ , a  $S_I$  cut-off value of  $0.00013 \text{ L} \cdot \text{mU} \cdot \text{min}^{-1}$  achieves a 50% sensitivity, 76% specificity, 4.8% PPV, and 98.3% NPV.

Even though  $S_I$  is generally lower at higher ss values, the distribution of  $S_I$  for each ss group overlaps too much in Figure 1 and Figure 2 with the non septic group. Therefore, using  $S_I$  level itself is not a completely effective sepsis biomarker. It should be noted that the improved modelling in this study has improved discrimination compared to prior results.

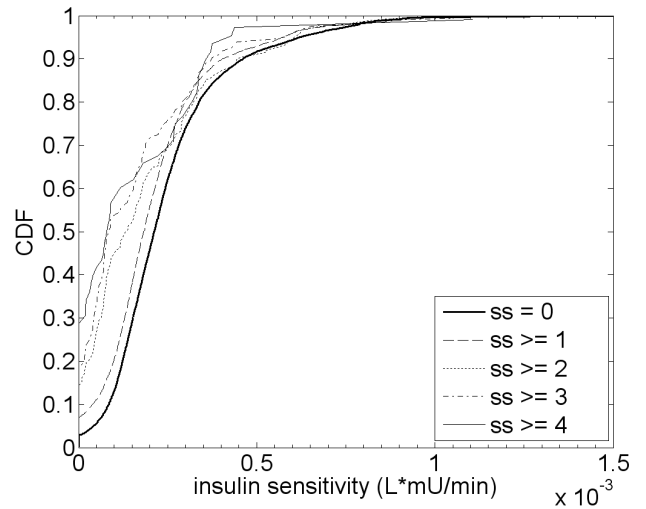


Fig. 1. Cumulative distribution function (CDF) of insulin sensitivity (SI), grouped by sepsis score (ss).

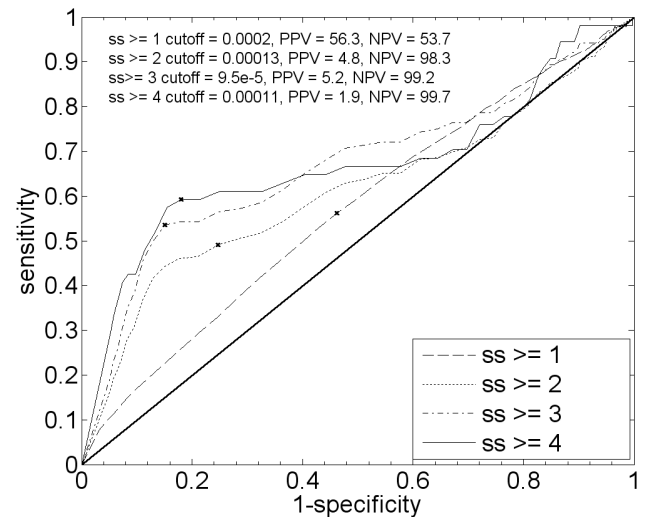


Fig. 2. Receiver operator characteristic (ROC) curve for SI biomarker, grouped by sepsis score (ss), with cutoff points (x).

#### 3.3 Clinical biomarker including $S_I$

Figure 3 shows the CDF of a biomarker combining  $S_I$  and other clinical factors, for each ss group. The clinical measurements used in the biomarker include temperature, heart rate, respiratory rate, blood pressure, and their respective rates of change.  $S_I$  is defined as in (1). The biomarker generally decreases with increasing sepsis severity. The discrimination between sepsis and non-septic groups is improved, as compared to Figure 1 using  $S_I$  only as a diagnostic test.

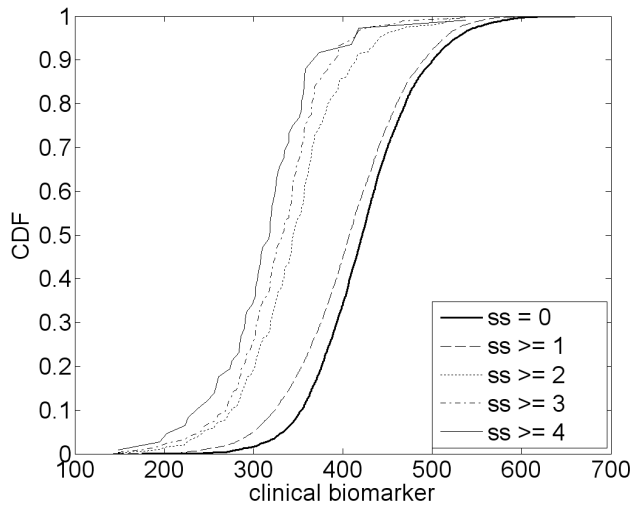


Fig. 3. Cumulative distribution function (CDF) of the clinical biomarker, grouped by sepsis score (ss).

Figure 4 shows the ROC curve for this biomarker. For  $ss \geq 2$ , the biomarker achieves 73% sensitivity, 80% specificity, 8.4% PPV, and 99.2% NPV. The addition of clinical measurements with  $S_1$  significantly improved the diagnostic test performance for sepsis, as compared to using  $S_1$  alone. In particular, the biomarker provides an effective negative predictive diagnosis for severe sepsis ( $ss = 2$ ), which was not achieved previously.

It is also clear comparing Figure 2 and Figure 4 that the discrimination between  $ss = 1$  and  $ss \geq 2$  is now far wider. Note that  $ss = 1$  is difficult to discriminate from  $ss = 0$  and simple, clinical SIRS. Hence, as seen in Figure 2 and Figure 4, its discrimination from  $ss = 0$  is still marginal.

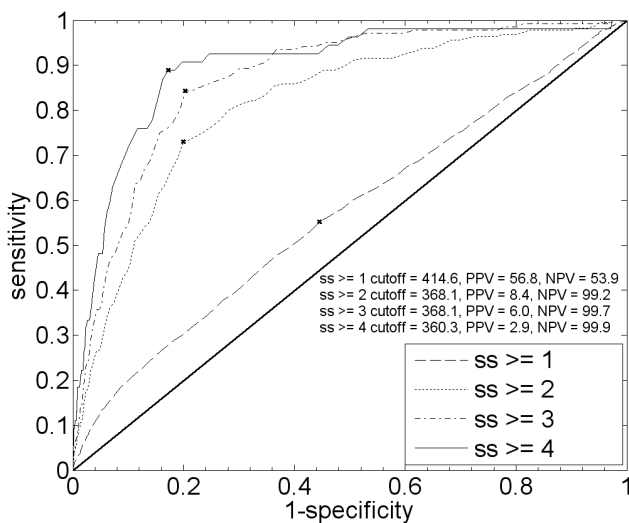


Fig. 4. Receiver operator characteristic (ROC) curve for the clinical biomarker, grouped by sepsis score (ss), with cutoff points (x).

Table 5 is a contingency table showing the biomarker diagnostic outcome for  $ss \geq 2$ . There are 9208 total hours of patient data. This data is classified into four categories using

sepsis score and biomarker test outcome: true positive (TP,  $n = 165$ ), false positive (FP,  $n = 1802$ ), false negative (FN,  $n = 61$ ), and true negative (TN,  $n = 7180$ ). There are 8982 hours when  $ss < 2$  and 226 hours when  $ss \geq 2$ . Using the biomarker, 7241 hours test negative and 1967 hours test positive.

Table 5. Contingency table

	$ss \geq 2$ 226 hours	$ss < 2$ 8982 hours	
test positive 1967 hours	TP = 165 (1.8%)	FP = 1802 (19.6%)	PPV 8.4%
test negative 7241 hours	FN = 61 (0.7%)	TN = 7180 (78%)	NPV 99.2%
total 9208 hours	sensitivity 73.0%	specificity 79.9%	

Note that these ratios also indicate the relative incidence and reflect clinical expectations with most sepsis not necessarily severe by hour. This last point is critical as most sepsis incidence is recorded by patients. By patient, the incidence of severe sepsis is 5-10% (Angus et al., 2001), which is reflected in this cohort. However, with rapid, aggressive treatment its incidence by hour is low. This low incidence is problematic in developing such a non-invasive and real-time clinical biomarker.

Figure 5 provides a visual presentation of clinical sepsis score and the biomarker performance. Most of the patient hours are  $ss < 2$  (TN + FP). Even though the biomarker correctly identifies the severity of sepsis 73% of the time when  $ss \geq 2$  and 80% of the time when  $ss < 2$ , the PPV stays low because the ratio of TP to test positive is limited by the ratio between  $ss \geq 2$  to  $ss < 2$ . Again, the mathematics indicate that relatively low incidence by hour, as seen in the 8982 hours of  $ss < 2$  and 4186 hours of  $ss = 0$ , hinders good PPV without nearly perfect specificity.

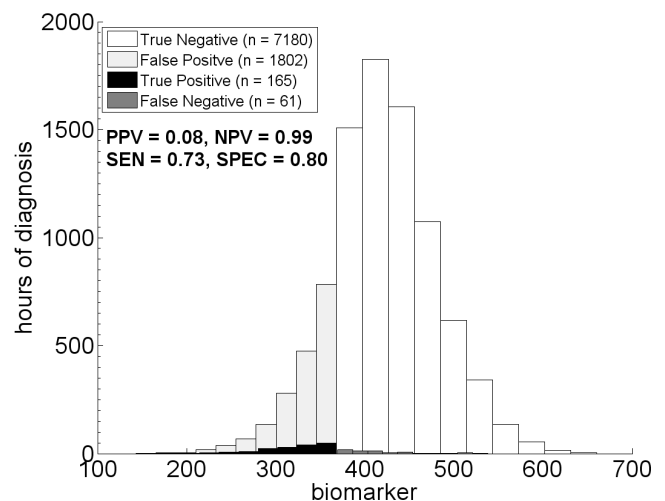


Fig. 5. Histogram of clinical biomarker data, grouped by contingency results.

### 3.4 Sepsis time course

Figure 6 effectively shows the probability of how  $ss$  changes from one hour to the next. The horizontal axis is the current hour  $ss$  and the vertical axis is the  $ss$  for the next hour. The majority of the patient data is when  $ss = 0$  and  $ss = 1$ .

Patients at  $ss = 1$  tend to stay at  $ss = 1$ , and patients having  $ss = 0$  tend to stay at  $ss = 0$ . Interestingly, when  $ss \geq 2$ , the highest probability is moving to  $ss = 1$  in the next hour. This set of results shows that if sepsis is detected at  $ss \geq 2$ , current rapid and aggressive ICU treatments are usually very effective in reducing the severity of the inflammatory responses.

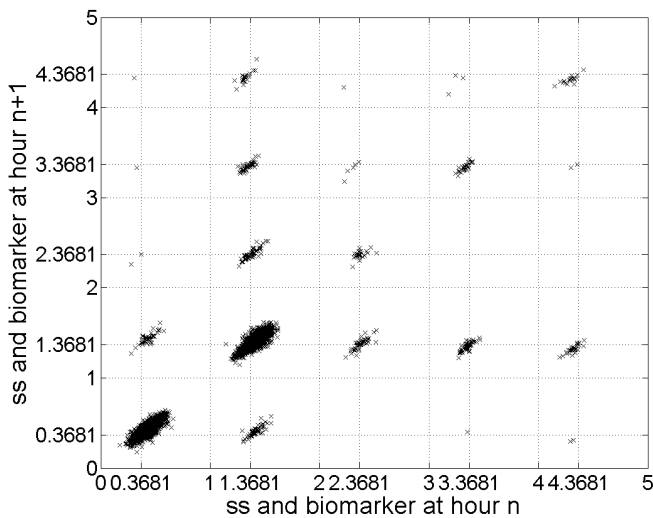


Fig. 6. Scatter plot of clinical biomarker variation from hour to hour with respect to sepsis score ( $ss$ ) (axis numbers =  $ss + \text{biomarker}/1000$ ).

### 3.5 Biomarker comparison

The clinical informative values a biomarker may provide in sepsis are: detection of infection; diagnosis of SIRS severity and infection progression; and patient treatment guidance, responsiveness, and prognosis. One such investigated biomarker is procalcitonin (PCT), which was first found elevated in sepsis in 1993 (Assicot et al. 1993). PCT is a precursor of the hormone calcitonin, synthesized by thyroid C cells, but in sepsis has an extra-tyroidal origin. Upon intravenous injection of endotoxin from *E. coli* in healthy volunteers, serum PCT becomes detectable after 4 hours, maintaining a plateau through 8 to 24 hours, following an increase of proinflammatory cytokines (Dandona 1994).

PCT can be measured from serum plasma by commercially available immunoluminometric assay kits such as LUMItest PCT (Brahms, Berlin, Germany) and Kryptor PCT (Brahms, Hennigsdorf, Germany). The use of PCT has been approved by the FDA “in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock”.

The reported diagnostic power of PCT from 25 studies using PCT (2,966 patients) as a diagnostic marker of sepsis, severe sepsis, or septic shock in the adult ICU or after surgery or multiple trauma, compared with nonseptic SIRS is sensitivity ranging from 42% to 97% or even 100% and specificity ranging from 48% to 100% (Uzzan et al. 2006). Optimal cutoff values for PCT, determined from ROC curves, ranged from 0.6 to 5 ng/mL.

PCT is generally only assessed once a day and thus cannot provide real-time detection. In contrast, the biomarker presented in this study is a real-time marker. In addition, all of these studies had some form of pre-screening for sepsis and/or SIRS biasing the sensitivity or specificity. The overall results reported are no better, and often worse, than those reported here.

Traditionally, diagnostic test results are based on a cut-off point. This method effectively treats all patients as a single, generic person with one clear cut-off point that distinguishes between normal and abnormal states. However, recent medical treatments have been moving towards patient customisation – tailoring treatments to patient needs (Chase et al., 2007a). Although this study has so far provided a sepsis biomarker that has a cut-off value which can differentiate  $ss \geq 2$  from  $ss < 2$  most of the time, this biomarker is also a time-varying value. As with most clinical measurements, this biomarker would have both inter- and intra-patient statistical distribution.

### 3.6 Future work

It is therefore of interest to further investigate how this biomarker changes through time for patients, and how much variability there is between patients. A means of normalizing patients and likely changes using stochastic models would improve biomarker performance. An observational study and follow-up of a biomarker for sepsis diagnosis in the ICU would provide the data needed for that analysis. Finally, the statistical model of a biomarker, like the one developed in this paper, may be more useful clinically by providing a probability analysis of disease progression in real-time.

## 4. CONCLUSIONS

Insulin sensitivity as a sepsis biomarker for diagnosis of severe sepsis achieves a 50% sensitivity, 76% specificity, 4.8% PPV, and 98.3% NPV at a  $S_I$  cut-off value of 0.00013  $L \cdot mU \cdot min^{-1}$ . A discriminating threshold was not found between the  $ss = 0$  and  $ss = 1$  cohorts due to patient population overlap. A clinical biomarker combining  $S_I$ , temperature, heart rate, respiratory rate, blood pressure, and the respective rate of change achieves 73% sensitivity, 80% specificity, 8.4% PPV, and 99.2% NPV, and thus an effective negative predictive diagnosis for severe sepsis.

PPV performance is low because the ratio of TP to test positive is limited by the ratio of hours between  $ss \geq 2$  to  $ss < 2$ . The majority of patient hours were  $ss < 2$ . However,

clinical biomarker data may provide patient-specific diagnosis, and effectively show the probability of sepsis time course from hour to hour. Real-time results may aid in the treatment and management of sepsis in the ICU. Future work includes an observational study and follow-up of a biomarker for sepsis diagnosis in the ICU.

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